Remarks

Amendments to the Claims

Claims 10 and 11 are amended to recite a method of "reducing neuronal cell death" rather than a method of "preventing" neuronal cell death. Paragraph [49] of the specification supports this amendment: "Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. . . . Such administrations can be used to reduce or eliminate cell death . . . ."

Dependent claims 12 and 18 (and withdrawn claims 13-17 and 19) are amended to delete "subject" and recite "mammal," which has antecedent basis in claims 10 and 11.

None of the amendments adds new matter.

The Rejection of Claims 10-12 and 18 Under 35 U.S.C. § 112 ¶ 1

Claims 10-12 and 18 stand rejected under 35 U.S.C. § 112 ¶ 1 as not enabled. Applicants respectfully traverse the rejection.

The enablement requirement of 35 U.S.C. § 112, first paragraph states that a patent specification must teach a person skilled in the relevant art how to make and use the invention claimed. The proper standard for determining whether the present specification meets the enablement requirement is whether any experimentation which may be needed to practice the methods of claims 10-12 and 18 is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

The U.S. Patent and Trademark Office has the initial burden to establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To make a *prima facie* case of non-

enablement using this standard, an Examiner must properly construe the claims and must weigh all the evidence and establish a reasonable basis to question the enablement provided in the specification for the claimed invention. M.P.E.P. §§ 2164.04 and 2164.05, 8th ed., August, 2005. In the present application, a *prima facie* case of non-enablement has not been made. The weight of evidence, including the teachings of the specification and the prior art – and including the references cited in the rejection – favors the conclusion that claims 10-12 and 18 are enabled.

The nature of the invention and the breadth of the claims

The rejected claims are directed to methods of reducing neuronal cell death in a mammal. The method of independent claim 10 comprises administering to the mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker (NM) protein selected from a recited group of proteins. The method of independent claim 11 comprises administering one of a recited group of neuronal marker proteins to a mammal. The pending claims encompass – but do not require – "preventing a disease associated with neuronal cell death." Office Action at page 4.

The state of the prior art and the predictability or unpredictability of the art

The Office Action devotes several pages to a discussion of prior art references it contends reflect the state of the prior art at the time the application was filed and describe various difficulties with achieving successful gene therapy:

- Orkin *et al.*, "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995;
- Goodman & Gilman's The Pharmacological Basis of Therapeutics, 1996;
- Marshall, *Science 269*, 1050-55, 1995;

- Verma & Sonyia, *Nature 389*, 239-42, 1997;
- Zabner *et al.*, *J. Biol. Chem. 270*, 18997-19007, 1995;
- Lechardeur *et al.*, *Gene Ther. 6*, 482-97, 1999;
- Tjuvajev *et al.*, *Cancer Research 59*, 5186-93, 1999; and
- Bramson *et al.*, *Gene Ther. 4*, 1069-76, 1997.

Each of these references was published between 1995 and 1999. The state of the art of gene therapy in 1995-1999 is not relevant to whether the claimed method was enabled at this application's July 13, 2003 priority date. It is the state of the art in July 2003 that is relevant to the enablement of claims 10-12 and 18. The following documents, which are listed in the accompanying Information Disclosure Statement, provide evidence that those skilled in the art in July 2003 were able to effectively transfer and express exogenous genes in neurons *in vivo*:

Auricchio *et al.*, "Exchange of surface proteins impacts on viral vector cellular specificity and transduction characteristics: the retina as a model," *Human Molecular Genetics 10*, 3075
Bankiewicz *et al.*, "Convection-enhanced delivery of AAV vector in parkinsonian monkeys; in vivo detection of gene expression and restoration of dopaminergic function using pro-drug approach," *Exp. Neurol. 164*, 2-14, July 2000 (abstract)
Biewenga *et al.*, "Plasmid-mediated gene transfer in neurons using the biolistics technique," *J. Neurosci. Methods 71*, 67-75, January 1997 (abstract)
Blesch *et al.*, "Modulation of neuronal survival and axonal growth in vivo by tetracycline-regulated neurotrophins expression," *Gene Therapy 8*, 954-60, June 2001 (abstract)
Blesch & Tuszynski, "GDNF gene delivery to injured adult CNS motor neurons promotes axonal growth, expression of the trophic neuropeptide CGRP, and cellular protection," *J. Comp. Neurol. 436*, 399-410, August 2001 (abstract)
Blits *et al.*, "Pharmacological, cell, and gene therapy strategies to promote spinal cord regeneration," *Cell Transplant. 11*, 593-613, 2002 (abstract)
Boviatsis *et al.*, "Gene transfer into experimental brain tumors mediated by adenovirus, herpes simplex virus and retrovirus vectors," *Hum. Gene Ther. 5*, 183-91, February 1994 (abstract)
Breakefield & DeLuca, "Herpes simplex virus for gene delivery to neurons," *New Biol. 3*, 203-18, March 1991 (abstract)
Chen *et al.*, "HSV amplicon-mediated neurotrphin-3 expression protects murine spiral ganglion neurons from cisplatin-induced damage," *Mol. Ther. 3*, 958-63, June 2001 (abstract)
Cheng *et al.*, "Human immunodeficiency virus type 2 (HIV-2) vector-mediated in vivo gene transfer into adult rabbit retina," *Curr. Eye Res. 24*, 196-201, March 2002 (abstract)
Davar *et al.*, "Comparative efficacy of expression of genes delivered to mouse sensory neurons with

herpes virus vectors," *J. Comp. Neurol. 339*, 3-11, January 1994 (abstract)
de Marco *et al.*, "MR imaging of gene delivery to the central nervous system with an artificial vector," *Radiology 208*, 65-71, July 1998 (abstract)
Di Polo *et al.*, "Prolonged delivery of brain-derived neurotrophic factor by adenovirus-infected Müller cells temporarily rescues injured retinal ganglion cells," *Proc. Natl. Acad. Sci. USA 95*, 3978-83, March 1998
Eberhardt *et al.*, "Protection by synergistic effects of adenovirus-mediated X-chromosome-linked inhibitor of apoptosis and glial cell line-derived neurotrophic factor gene transfer in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease," J Neurosci. 2000 Dec 15;20(24):9126-34
Fathallah-Shaykh *et al.*, "Gene Transfer into Brain Parenchyma Elicits Antitumor Effects," *Cancer Res. 60*, 1797-99, April 1, 2000
Garcia-Valenzuela *et al.*, "Axon-mediated gene transfer of retinal ganglion cells in vivo," *J. Neurobiol. 32*, 111-22, January 1997 (abstract)
Haas *et al.*, "Single-cell electroporation for gene transfer in vivo," *Neuron 29*, 583-91, March 2001 (abstract)
Hagihara *et al.*, "Widespread gene transfection into the central nervous system of primates," *Gene Ther. 7*, 759-63, May 2000 (abstract)
Han *et al.*, "Transgene expression in the guinea pig cochlea mediated by a Lentivirus-derived gene transfer vector," *Hum. Gene Ther. 10*, 1867-73, July 20, 1999 (abstract)
Hecker *et al.*, "Nonviral gene delivery to the lateral ventricles in rat brain: initial evidence for widespread distribution and expression in the central nervous system," *Mol. Ther. 3*, 375-84, March 2001 (abstract)
Hossain *et al.*, "Human FGF-1 gene delivery protects against quinolinate-induced striatal and hippocampal injury in neonatal rats," *Eur. J. Neurosci. 10*, 2490-99, August 1998 (abstract)
Isenmann *et al.*, "Short communication: protection of axotomized retinal ganglion cells by adenovirally delivered BDNF in vivo," *Eur. J. Neurosci. 10*, 2751-56, August 1998 (abstract)
Johnston *et al.*, "Delivery of human fibroblast growth factor-1 gene to brain by modified rat brain endothelial cells," *J. Neurochem. 67*, 1643-52, October 1996 (abstract)
Joung *et al.*, "Effective gene transfer into regenerating sciatic nerves by adenoviral vectors: potentials for gene therapy of peripheral nerve injury," *Mol. Cells. 10*, 540-45, October 2000 (abstract)
Kaspar *et al.*, "Targeted retrograde gene delivery for neuronal protection," *Mol. Ther. 5*, 50-56, January 2002 (abstract)
Keir *et al.*, "Adeno-associated virus-mediated delivery of glial cell line-derived neurotrophic factor protects motor neuron-like cells from apoptosis," *J. Neuroviol. 7*, 437-46, October 2001 (abstract)
Knight *et al.*, "Non-viral neuronal gene delivery mediated by the H_C fragment of tetanus toxin," *Eur. J. Biochem. 259*, 762-69, 1999
Kugler *et al.*, "Transduction of axotomized retinal ganglion cells by adenoviral vector administration at the optic nerve stump: an in vivo model system for the inhibition of neuronal apoptotic cell death," *Gene Ther. 6*, 1759-67, October 1999 (abstract)
Lachman & Efstathiou, "Utilization of the Herpex Simplex Virus Type 1 Latency-Associated Regulatory Region To Drive Stable Reporter Gene Expression in the Nervous System," *J. Virol. 71*, 3197-207, April 1997
Lilley *et al.*, "Multiple Immediate-Early Gene-Deficient Herpes Simplex Virus Vectors Allowing

Efficient Gene Delivery to Neurons in Culture and Widespread Gene Delivery to the Central Nervous System In Vivo," *J. Virol. 75*, 4343-56, May 2001
Liu *et al.*, "Application of recombinant adenovirus for in vivo gene delivery to spinal cord," *Brain Res. 768*, 19-29, September 12, 1997 (abstract)
Mandel *et al.*, "Nerve growth factor expressed in the medial septum following in vivo gene delivery using a recombinant adeno-associated viral vector protects cholinergic neurons from fimbria-fornix lesion-induced degeneration," *Exp. Neurol. 155*, 59-64, January 1999 (abstract)
Naldini *et al.*, "Efficient transfer, integration, and sustained long-term expression of the transgene in adult rat brains injected with a lentiviral vector," *Proc. Natl. Acad. Sci. USA 93*, 11382-88, October 1996 (presented at a conference held June 9-11, 1996)
Naldini *et al.*, "In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector," *Science 272*, 263-67, April 12, 1996 (abstract)
Ogueta *et al.*, "The Human cGMP-PDE β-Subunit Promoter Region Directs Expression of the Gene to Mouse Photoreceptors," *Investigative Ophthalmology & Visual Science 41*, 4059-63, December 2000
Palmer *et al.*, "Development and Optimization of Herpes Simplex Virus Vectors for Multiple Long-Term Gene Delivery to the Peripheral Nervous System," *J. Virol. 74*, 5604-18, June 2000
Perrelet *et al.*, "IAP family proteins delay motoneuron cell death in vivo," Eur J Neurosci. 2000 Jun;12(6):2059-67
Sarkis *et al.*, "Efficient transduction of neural cells *in vitro* and *in vivo* by a baculovirus-derived vector," *Proc. Natl. Acad. Sci. USA 97*, 14638-43, December 19, 2000
Schneider *et al.*, "Retargeting of adenoviral vectors to neurons using the Hc fragment of tetanus toxin," *Gene Ther. 7*, 1584-92, September 2000 (abstract)
Sinnayah *et al.*, "Selective Gene Transfer to Key Cardiovascular Regions of the Brain: Comparison of Two Viral Vector Systems," *Hypertension 39*, 603-08, 2002
Taylor, "Cell vehicles for gene transfer to the brain," *Neuromuscul. Disord. 7*, 343-51, July 1997 (abstract)
Terashima *et al.*, "Retrograde and anterograde labeling of cerebellar afferent projection by the injection of recombinant adenoviral vectors into the mouse cerebellar cortex," *Anat. Embryol. 196*, 363-82, November 1997 (abstract)
Wu *et al.*, "An AAV promoter-driven neuropeptide Y gene delivery system using Sendai virosomes for neurons and rat brain," *Gene Ther. 3*, 246-53, March 1996 (abstract)
Zhang *et al.*, "Protective effects of adenoviral cardiotrophin-1 gene transfer on rubrospinal neurons after spinal cord injury in adult rats," Neurotox Res. 2003;5(7):539-48

The Office Action cites Shah as generically teaching various difficulties with respect to administration of proteins. However, the following documents, which are listed in the accompanying Information Disclosure Statement, provide evidence that those skilled in the art in July 2003 were able to effectively administer proteins to reduce or prevent neuronal death *in vivo*:

Giehl & Tetzlaff, "BDNF and NT-3, but not NGF, prevent axotomy-induced death of rat corticospinal neurons in vivo," *Eur. J. Neurosci. 7*, 1167-75, June 1996 (abstract)
Hoffman *et al.*, "NGF released from a polymer matrix prevents loss of ChAT expression in basal forebrain neurons following a fimbria-fornix lesion," *Exp. Neurol. 110*, 39-44, October 1990 (abstract)
Hughes *et al.*, "Axotomized septal cholinergic neurons rescued by nerve growth factor or neurotrphin-4/5 fail to express the inducible transcription factor c-Jun," *Neurosci. 78*, 1037-49, June 1997 (abstract)
Kawaja *et al.*, "Somatic gene transfer of nerve growth factor promotes the survival of axotomized septal neurons and the regeneration of their axons in adult rats," *J. Neurosci. 12*, 2849-64, July 1992 (abstract)
Knusel *et al.*, "Brain-derived neurotrophic factor administration protects basal forebrain cholinergic but not nigral dopaminergic neurons from degenerative changes after axotomy in the adult rat brain," *J. Neurosci. 12*, 4391-402, November 1992 (abstract)
Koliatsos *et al.*, "Mouse Nerve Growth Factor Prevents Degeneration of Axotomized Basal Forebrain Cholinergic Neurons in the Monkey," *J. Neurosci. 10*, 3801-13, December 1990
Kromer, "Nerve growth factor treatment after brain injury prevents neuronal death," *Science 235*, 214-16, January 1987 (abstract)
Lucidi-Phillipi *et al.*, "TrkA activation is sufficient to rescue axotomized cholinergic neurons," *Neuron 16*, 653-63, March 1996 (abstract)
Morse, "Brain-derived Neurotrophic Factor (BDNF) Prevents the Degeneration of Medial Septal Cholinergic Neurons following Fimbria Transection," *J. Neurosci. 13*, 4146-56, October 1993
Pean *et al.*, "Intraseptal implantation of NGF-releasing microspheres promote the survival of axotomized cholinergic neurons," *Biomaterials 21*, 2097-101, October 2000 (abstract)
Takei *et al.*, "Pituitary adenylate cyclase-activating polypeptide promotes the survival of basal forebrain cholinergic neurons in vitro and in vivo: comparison with effects of nerve growth factor," *Eur. J. Neurosci. 12*, 2273-80, July 2000 (abstract)
Wilcox *et al.*, "Nerve growth factor prevents apoptotic cell death in injured central cholinergic neurons," *J. Comp. Neurol. 359*, 573-85, September 1995 (abstract)
Williams *et al.*, "Glial cell line-derived neurotrophic factor sustains axotomized basal forebrain cholinergic neurons in vivo: dose-response comparison to nerve growth factor and brain-derived neurotrophic factor," *J. Pharmacol. Exp. Therp. 277*, 1140-51, May 1996 (abstract)
Williams *et al.*, "Continuous infusion of nerve growth factor prevents basal forebrain neuronal death after fimbria fornix transection," *pnas 83*, 9231-35, December 1986
Xu *et al.*, "Polyphosphoester microspheres for sustained release of biologically active nerve growth factor," *Biomaterials 23*, 3765-72, September 2002 (abstract)
Yasuno *et al.*, "Nerve growth factor applied onto the olfactory epithelium alleviates degenerative changes of the olfactory receptor neurons following axotomy," *Brain Res. 887*, 53-62, December 22, 2000 (abstract)

The Office Action cites Yu and Thomas as evidence that clinical therapeutic success of various gene therapy methods is not predictable. Office Action at page 9. In determining enablement, the U.S. Patent and Trademark Office should not be concerned with demonstrations of therapeutic success. By doing so, the Office "confuses the requirements under the law for

obtaining a patent with the requirements for obtaining government approval to market [a therapeutic invention]." *In re Brana*, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). It is well settled that a therapeutic invention need not be refined to the point where clinical efficacy in patients can be demonstrated in order to be patentable. *Brana*, 34 U.S.P.Q.2d at 1442. The Office cannot impose a requirement that the claimed methods be shown to be clinically effective, because such a requirement is not consistent with the law.

The Office Action also spends several pages discussing various ways in which cell death can occur. The Office Action concludes that because "neuronal death is unlikely to have a single, discrete pathway," use of a nucleic acid molecule expressing a neuronal marker "to prevent a neurodegenerative disease" is unpredictable. First, the claims do not require prevention of a neurodegenerative disease. Second, the specification teaches that expression of the recited neuronal marker proteins is specifically decreased after axiotomy (which causes neuronal cell death) and that administration of a nucleic acid molecule expressing the recited neuronal marker proteins can be used to reduce neuronal cell death. Understanding the mechanism by which any particular neuronal marker protein reduces neuronal cell death is neither relevant nor required for enablement.

> The quantity of experimentation necessary, the amount of direction or guidance provided in the specification, and the presence or absence of working examples

The standard for whether a claim is enabled is whether any experimentation that must be carried out is undue. *Mineral Separation v. Hyde*, 242 U.S. at 270. However, this does not mean that no experimentation at all is permitted. Thus, even if routine experimentation were required to optimize the claimed methods, that does not make the experimentation undue:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 169 U.S.P.Q. 759 (2d. Cir. 1971), *cert. denied*, 404 U.S. 1018 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. In re Rainer, 52 CCPQ 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re Colianni, [561 F.2d 220, 195 US.P.Q. 150 (C.C.P.A. 1977)].

Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. Interf. 1982).

The specification is addressed to those skilled in the art. The law is clear that the specification need not provide knowledge that is generally known by those skilled in the art. Applicants can properly rely on common knowledge in the art to bolster and supplement the teachings of the specification. *Genentech Inc. v. Novo Nordisk A/S*, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). The specification and the references discussed above demonstrate that those skilled in the art at the July 2002 priority date of this application had a variety of tools available with which to successfully deliver to a target cell a nucleic acid molecule encoding a desired protein.

Finally, the Office Action faults the specification for not providing working examples. Working examples are not required to enable an invention. *In re Long*, 368 F.2d 892, 895, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). In view of the extensive teachings in the prior art regarding *in vivo* gene transfer in general and the explicit teachings of the specification, the lack of *in vivo* working examples should not be given undue weight.

The level of skill in the art

The Office Action acknowledges that the level of skill in the art was high at the time the application was filed. This factor weighs in favor of enablement, especially when taken together with the teachings of the specification and prior art discussed above.

All the evidence of record must be considered in its entirety. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). The Office has not properly weighed the evidence of record, including the relevance of the documents cited in the Office Action. When correctly analyzed, the weight of evidence of record in this application favors a finding of enablement of claims 10-12 and 18.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Date: July 5, 2006

By: 

Lisa M. Hemmendinger
Registration No. 42,653

Customer No. 22907